#4009 Medications for nasal and sinus irrigation
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The state of literature on CRS

There is a paucity of clinical trials of nasal medications for CRS both in children and adults. Treatment guidelines have been promulgated based on level of evidence as well as expert opinion. In most cases, expert opinion rather than high level evidence guides the recommendations (1-5).

We will focus on treatment of chronic rhinosinusitis (CRS) or acute exacerbations of CRS. Most studies of topical antibiotics and topical antifungals have been conduced in patients who had previous endoscopic surgery.

Saline nasal irrigations

Saline nasal irrigations are recommended by most expert panels, although the level of evidence for their efficacy is relatively weak. Reported physiological effects also include direct cleansing of irrigation, removal of inflammatory mediators, and stabilization of mucosal function.

A variety of proprietary devices and dry salt powders are on the market. Bulb syringes may be used as well for delivery. The "original" Neti-pot type irrigation devices require the patient to tilt their head to the side and saline is instilled using gravity. Newer devices include "squeeze bottles," nebulizers, and smaller bottles that may be used to deliver medications.

How do I instruct patients to use saline irrigation?

It is important to remind people to use warm water and explain proper head position so the solution does not go down the back of the throat.

The AAAAI website has a patient education handout designed for this purpose. It explains to patients how and why to use saline irrigation and contains a buffered salt solution recipe. It is available on-line at: http://www.aaaai.org/patients/publicedmat/sinusitis/rinse_recipe.pdf
http://www.fammed.wisc.edu/research/past-projects/nasal-irrigation (video)

Should isotonic or hypertonic solutions be used?

There are conflicting *in vivo* and *in vitro* data regarding the effect of isotonic and hypertonic saline on mucociliary clearance and ciliary beat frequency (6-8). Hypertonic solutions may cause osmotic shrinkage of nasal mucosa and improved endoscopic findings (6), and some but not all studies suggest it to be superior to physiologic saline. Greater than 3% saline may cause nasal irritation and other adverse effects. Some studies have failed to show benefit from saline rinses (9).

Rationale for use of topical antibiotics for CRS

Bacterial contributions to CRS may occur in the form of: occult infection s/a anaerobic bacteria, bacterial colonization with commensual organisms, s/a coagulase-negative Staphylococci, osteiitis, biofilms and culture-proven infection with a pathogen.

Not all CRS patients are infected. However, a subset is colonized with *Staphylococcus aureus*, MRSA, or gram-negative rods, including *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Serratia marcescens*, etc. Infection/colonization with these organisms likely contributes to ongoing symptoms, although there may be an underlying process such as eosinophilic inflammation or even fungal colonization. These are often the most "refractory" CRS cases and the ones in whom topical antibiotics are the most helpful.

Most topical antibiotic studies have been prospective observational studies only, not double-blind or placebo-controlled (10,11). The study population included postoperative patients only. The treatment involved a nebulized antibiotic for 3-6 weeks. Excellent to good improvement was reported in 82% of cases (10). Endoscopic improvement and an increase in infection-free interval after treatment was reported in one study (11). Both studies reported a low rate of side effects.

A recent systematic review of topical antimicrobials for CRS concluded that there is some evidence for the use of antibiotic nasal irrigations or nebulizations (12). The highest level of evidence exists for studies of postsurgical patients and culture-directed therapy. Both stable and acute exacerbations of CRS may benefit. Most studies are not randomized or placebo-controlled. More recent examples include the study of mupiricin irrigations for refractory CRS patients with culture-proven Staphylococcus aureus infection (13). Topical gentamycin or tobramycin 80 mg/liter irrigation is also useful for this purpose (14). Twice daily irrigation with gentamicin for 3 - 15 weeks caused low but measurable systemic absorption with blood levels ranging from .3 - .7 mcg/ml) (15). Also, sensorineural hearing loss was noted in 23% of CF patients who had used many irrigations (16).

Topical antibiotics can be administered with or without a nebulizer. Delivery of antibiotic to the sphenoethmoidal region is challenging and not recommended to be done with aminoglycosides because of potential ototoxicity. Duration of treatment should be at least 3 weeks, but some patients require chronic treatment.

Topical baby shampoo (a putative "biofilm buster")

Chemical surfactants have been suggested as a possible means to remove biofilm. One percent baby shampoo in normal saline was found to inhibit Pseudomonas biofilm formation *in vitro*. However, baby shampoo had no effect on the eradication of preformed Pseudomonas biofilms. An open label study was conducted in 18 patients with CRS using 1% baby shampoo solution (17). Two patients discontinued use because of minor nasal and skin irritations, 46.6% of patients experienced an overall improvement in their subjective symptoms, and 60% of patients noted improvement in symptoms of thickened mucus and postnasal drainage. Neilmed company recently came out with a commercially available surfactant-containing product named SinuSurf.

Antifungal treatment

Ponikau et al (18) were the first group to report a DBPCT of amphotericin B nasal irrigations. The study involved 24 patients, with patients receiving Amphotericin B 250 mg/liter nasal irrigation bid or a matching placebo for 6 months. In the study there was no distinction between CRSsNP vs CRScNP, however all patients had previous surgery. The extent of sinus opacification was determined by quantification of sinus mucosal thickening by "volumetric" measurement. Amphotericin B resulted in a 9% regression in sinus mucosal thickening versus a 2.5% worsening on placebo.

Two subsequent anti-fungal studies were negative. One involved use of an amphotericin B nasal spray for 8 wks. This treatment failed to improve sinus CT score (19). A study of systemic terbinafine at an oral dose of 625 mg daily for 8 wks also failed to improve sinus CT (20). Most recently, a DBPCT study by Ebbens et al (21) failed to show benefit from amphotericin B nasal irrigations 100 mg/liter using a study designed that was intended to reproduce the Ponikau study. However, there were a few differences in the studies that may have impacted the results, most importantly a difference in the amphotericin B concentration and a difference in the diluent used. Also, there was a much higher placebo response rate in the Ebbens et al study. All antifungal trials suffer from a lack of methods to confirm the presence of fungal immune hyperresponsiveness in patients enrolled in the studies.

Use of topical steroid rinses

A12-week, DBPCT demonstrated the benefit of using topical corticosteroid nasal drops for treatment of established nasal polyps (22). In this study, subjects were instructed to lie on their back in a bed with their heads hanging down in an inverted vertical position over the edge of the bed while drops of fluticasone propionate were administrated 200 µg per nostril once daily. They remained in this position for 2 minutes. The primary efficacy endpoint was based on a complicated scoring method that took into consideration patients' symptoms, sinus computed tomography (CT) score, and the physician's impression of the patient's need for sinus surgery. Fluticasone nasal drops reduced the need for sinus surgery, improved hyposmia and decreased nasal polyp volume.

Pulmicort Respules (aqueous budesonide) can be used "off-label" similar to the fluticasone nasal drops. The success of this treatment depends on delivery of the topical steroid to the polyp and polypoid tissue near the sinus ostia and in the sinus cavities. Usually a 0.5-mg Respule is mixed with one teaspoon of saline, and this mixture is instilled in the right nostril once daily first in the head down forward, then right lateral supine position, and finally in the supine position, each for 1–2 minutes, following which the remaining nasal solution is expelled from the nose. The procedure is then repeated in the left nostril (23). Many patients respond to this treatment. However, a controlled clinical trial has not been performed, and the long-term safety of this procedure has not been established. The clinician should be mindful to periodically evaluate the patient for possible systemic effects of the budesonide, including an increase in intraocular pressure.

A reasonable initial treatment of CRS is to start with the topical steroid rinse. Patient should be reassessed in 2-3 months. If persistent mucosal inflammation and sinus purulence are present, bacterial cultures should be obtained, and appropriate treatment should be given. If persistent mucosal inflammation is present in the absence of bacterial infection, I usually start topical antifungal treatment in conjunction with the topical steroid rinse and reassess in 2-3 months.

Are there safety concerns with using steroids with nasal saline rinses?

The use of budesonide, fluticasone or other steroids for sinus irrigation is off-label. Budesonide respules 0.25 mg/per nostril daily for 30 days using the above delivery technique was studied in nine adults with chronic sinusitis. This dosage did not suppress the HPA axis and significantly improved sinusitis health status (24). Wight et al. demonstrated "no serious adverse effects" with using 800 mcg/day of budesonide intranasally during a 12 week cross-over study (25). Long-term use could adversely affect the HPA axis and side effects should be monitored.

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